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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,403	11/27/2001	Hayat Onyuksel	27611/36927	2554

4743 7590 03/11/2004

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT

PAPER NUMBER

1615

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,403	ONYUKSEL ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 February 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5,6 and 10-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5,6 and 10-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The request for the extension of time and the filing of the exhibits both dated 2-9-04 are acknowledged.

Claims included in the prosecution are 5-6 and 10-12.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 5-6 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims are drawn to the treatment of at least 26 disease conditions and many of which are not even connected. The causes of many of the claimed diseases are not even known and many are poorly understood (Alzheimer's for example). The active agents apparently useful in the invention as recited in the claims are "VIP/glucagon/secretin family of peptides including peptide fragments and analogs". In the paragraph bridging pages 1 and 2 of the specification, applicant lists numerous number of proteins and peptides, which apparently belong to the class of this family.

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Applicant's own statements in the specification indicate that there is unpredictability in the art. While VIP appears to play a major role in regulating a variety of important functions and the deficiency of VIP has been linked to the pathogenesis of certain diseases, excess VIP also appears to be linked to the pathogenesis of some diseases (specification on pages 6 and 7). Instant specification provides no working examples either in vitro or in vivo for the variety of the disease conditions claimed using a variety of the active agents coming under the umbrella of VIP/glucagon/secratin family of peptides including peptide fragments and analogs'. Since there is unpredictability in the art of the treatment of the claimed diseases using the free active agents themselves, treatment of diseases using micelles containing active agents claimed is also unpredictable.

Broad claims must have broad basis of support in the specification; in the absence of such support, claims must be limited to specific disease(s) and specific active agent(s) disclosed as having the claimed treatment ability. It would require undue experimentation by one of ordinary skill in the art to select an active agent and practice the invention.

Applicant's arguments based on the submitted exhibits are fully considered, but are not found to be persuasive for the following reasons. The references of Wilson, and Melanson show the treatment of asthma using glucagons. Similarly, the reference of Bundgaard apparently teach the pretreatment of exercise-induced asthma with VIP. The reference of Reshef deals with impotence using stearyl-norleucine-VIP, but not VIP itself. The rest of the references mostly are concerned with

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biochemical studies involving VIP, but do not show the effectiveness of VIP in the treatment of various diseases claimed. The rejection based on 'There is no definition or explanation as to what come under the category of 'peptide fragments and analogs' is withdrawn. The rest of the rejection is maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 5-6 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawai (5,376,637) in combination with Trubetskoy (Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 1995) of record and either Burke (5,736,156) or EP 0 721 776 or Zhang (Internat. J. Of Pharmaceutics, 1996).

Sawai teaches that pharmaceutical composition containing VIP and a surfactant and a method of treatment of asthma (note the abstract and claim 1). What is lacking in Sawai is the specific teaching of the use of micelles containing VIP (although surfactants form micelles in aqueous solutions).

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Trubetskoy discloses that polymer derivatized lipids such as PEO-phosphatidylethanolamine form micelles and such micelles can be used to solubilize poorly soluble or amphipathic substances (pages 452-453). The active agent however, was not added after the formation of micelles.

Burke while disclosing a process of preparation of micelles and liposomes teaches that the active agent can be loaded to surfactant micelles after the preparation of the micelles (Examples 8-10).

Zhang similarly teaches that active agents such as taxol associate strongly to PEG containing polymer micelles (abstract).

EP similarly teaches that there is an electrostatic bonding when a drug is added to the macromolecular mPEG containing polymeric micelles (abstract, and examples).

The use of PEG containing polymeric compounds as the carrier of amphipathic VIP of Sawai for the treatment of asthma would have been obvious to one of ordinary skill in the art since Trubetskoy teaches that these compounds form micelles and solubilize poorly soluble or amphipathic compounds. One skilled in the art would be motivated to use this surfactant since PEG appears to increase the blood circulation time of drug carrier systems as evidenced from the teachings of Zhang (page 196, col. 1). The addition of VIP after the formation of micelles would have been obvious to one of ordinary skill in the art since the references of Burke, Zhang and EP all show that the active agent can be loaded onto the micelles; one of ordinary skill in the art would expect at least similar results.

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Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that in order to render a claimed invention obvious, the cited art not only has to 1) teach or suggest every element of the claimed invention; 2) must also provide some suggestion or motivation to modify the references to arrive at the claimed invention and 3) there must be some reasonable expectation of success of such modification and that the disclosures of Sawai, Trubetskoy, Burke, EO and Zhang fail to meet the criteria. The examiner disagrees. With respect to 1) the combination of the references is suggestive of every element of the claimed micelles. With regard to point 2): - the examiner has clearly set forth the motivation to combine the references. In instant case, the reference of Sawai teaches claimed VIP in a surfactant preparation for the treatment of disease, asthma. The secondary references of Trubetskoy and Zhang provide motivation to use micelles formed from hydrophilic polymer (to solubilizer poorly soluble or amphipathic substances and the association of active agents with surfactant micelles). The reference of Burke provides motivation to load active agent after the formation of the micelles. With regard to applicant's point 3 that there must be some reasonable expectation of success of such modification, the following is the examiner's position. As applicant himself argues from the literature evidence that the diseases claimed are VIP and glucagons treatable diseases and applicant himself has not provided evidence to show that micelle incorporated VIP is better than VIP itself in terms of various diseases claimed (AIDS for instance). The prior art of Sawai cited above, clearly shows the efficacy of VIP-surfactant combination in the treatment of asthma and that of EP that the bonding of a protein with the hydrophilic polymer

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provides stability to easily decomposable protein in vivo. The reference of Burke similarly is clearly suggestive of the stability of drugs in combination with micelles. Therefore, one of ordinary skill in the art would expect the micelles to provide stability to VIP (which is a protein) from in vivo degradation and therefore preserve its functional activity. The criteria for 'reasonable expectation of success' thus, are met from the combination of references.

Applicant's argument that one of the essential features of the present invention is that the micelles produced by the recited method must be sterically stabilized is not persuasive since Zhang is clearly indicative of the literature evidence that PEG coating increases the blood circulation time of Nan spheres due to the dramatically decrease by the reticuloendothelial system (page 196, col. 1). Applicant's arguments that there is nothing in the cited references to show that the micelle composition is biologically active are not found to be persuasive since as pointed out above, EP is suggestive of micelle carriers preventing the degradation of the easily decomposable proteins. Therefore, one would reasonably expect the biological activity of VIP to be preserved by the micelles. Furthermore, the references of Sawai show that the activity of VIP is preserved when it is administered together with a surfactant.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.



Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK